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Stress Testing

Exercise-Induced U-Wave Alterations as a Marker of Well-Developed and Well-Functioning Collateral Vessels in Patients With Effort Angina

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OBJECTIVES We sought to determine whether exercise-induced U-wave alterations are observed in association with well-developed and well-functioning collateral vessels.

BACKGROUND Although exercise-induced electrocardiographic (ECG) U-wave alterations including negative and prominent U waves have been established as a marker of significant or critical narrowing of a major coronary artery, the relation between this finding and the degree of collateral development has not yet been determined.

METHODS Patients with stable effort angina were divided into two groups according to the presence (group A, n = 46) or absence (group B, n = 79) of exercise-induced either negative or prominent U waves in the precordial leads; the clinical profiles, coronary angiographic findings and also ischemic status during 60 s of coronary balloon occlusion were compared between the two groups.

RESULTS The incidence of severe angina (CCS [Canadian Cardiovascular Society] class III or IV) was higher ($p < 0.05$) in group A (52%) than in group B (32%) patients. Good collateral vessels (Rentrop grade 2 or 3) into the perfusion territory of the culprit vessel were observed more frequently ($p < 0.05$) in group A (70%) than in group B (43%) patients. Coronary balloon angioplasty was carried out in 23 patients of group A and 40 patients of group B. Both ischemic ST changes (52% vs. 85%) and angina (57% vs. 80%) during balloon inflation were less ($p < 0.05$) frequently observed in group A than in group B. The incidence of no apparent myocardial ischemia with ST deviation or angina during the balloon inflation was higher ($p < 0.05$) in group A (39%) than in group B (10%) patients. In the prediction of the absence of myocardial ischemia during balloon inflation by the presence of exercise-induced U-wave alterations, the sensitivity was 69% (9/13) and the specificity was 72% (36/50) in the study patients.

CONCLUSIONS Exercise-induced U-wave alterations are a marker for well-developed collateral circulation in patients with stable but severe effort angina. This finding is also highly predictive of the absence of myocardial ischemia during transient coronary balloon occlusion and possibly of low-risk for development of acute myocardial infarction or hemodynamic instability upon abrupt closure of the culprit coronary artery. (J Am Coll Cardiol 2000;35:757–63) © 2000 by the American College of Cardiology

The appearance of electrocardiographic (ECG) negative U waves in precordial leads during exercise is known to be a marker for anterior myocardial ischemia and is highly predictive of significant disease of the proximal portion of the left anterior descending coronary artery (LAD) (1–4). Also, exercise-induced prominent U waves in precordial leads have been recently proposed as reciprocal changes for negative U waves in inferoposterior ischemia (5). This finding was reported to be a specific marker of significant narrowing of the left circumflex or right coronary artery (5).

Rentrop et al. (6) and Yoshida et al. (7) suggested a positive relation between lesion severity and collateral development. However, the angiographic development of collateral vessels and their function in patients with exercise-induced U-wave changes remain to be elucidated. Recently, Chikamori et al. (8) reported that in patients with anterior wall myocardial infarction (MI), angiographic findings in patients with exercise-induced appearance of negative U waves in precordial leads revealed more extensive coronary artery disease and higher grade of LAD narrowing, combined with well-developed collateral circulation to this

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JACC Vol. 35, No. 3, 2000
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Abbreviations and Acronyms

ECG	= electrocardiogram, electrocardiographic
CCS	= Canadian Cardiovascular Society
LAD	= left anterior descending coronary artery
MI	= myocardial infarction
TIMI	= Thrombolysis in Myocardial Infarction trial

artery, whereas in patients without anterior wall MI, no difference in angiographic findings was detected between those with and without exercise-induced negative U waves. In the present study, we examined whether the ECG finding of exercise-induced U-wave changes including both negative and prominent U waves in precordial leads is a marker of well-developed collateral vessels in patients with stable effort angina or symptomatic myocardial ischemia. Furthermore, in the patients undergoing coronary balloon angioplasty, the incidence of the absence of ischemic ST deviation during the first minute of the balloon inflation was compared between subjects with and without exercise-induced U-wave changes to evaluate the protective function of the collateral circulation against ischemia during the interruption of anterograde coronary flow.

METHODS

The study population consisted of 125 consecutive patients (90 men and 35 women, mean age 62 ± 10 years) with stable effort angina pectoris with significant ST-segment elevation or depression of ≥0.1 mV during treadmill exercise stress testing. All the patients had a significant (>75% of luminal narrowing) organic coronary stenosis demonstrated by coronary arteriography but without conduction disturbance or ST-segment abnormalities that would preclude ECG assessment of ischemia. Patients with angina at rest had been excluded from the study. Fifty-two patients (42%) had a history of previous MI. According to the classification proposed by the Canadian Cardiovascular Society (CCS) (9), 49 (39%) had severe angina of class III or class IV. Among the study population, 63 patients (48 men and 15 women, mean age 60 ± 9 years) underwent coronary angioplasty for treatment of angina pectoris and became the subjects for the subsequent analysis.

Exercise-stress testing. Treadmill exercise stress testing was performed with the patient off cardioactive medications using the standard Bruce protocol within a week prior to coronary arteriography (10). Chest pain, ST-segment elevation or depression, and age-predicted maximal heart rate were regarded as indications for stopping exercise. Heart rate, blood pressure, 12-lead ECG, and symptoms at rest, during exercise, and for the first 6 min after exercise were recorded. Electrocardiography soon after exercise was compared with that performed at rest for the magnitude of ST-segment shift, which was measured at 80 ms after the J point. An ST-segment depression of ≥0.1 mV was considered significant for myocardial ischemia. The magnitude of negative U waves was also measured, with TP segment as the baseline when the heart rate slowed down after exercise. Negative U waves were considered to be significant if there was a discrete, negative deflection of more than 0.05 mV in depth within the TP segment (2,3). Exclusion of terminal T-wave negativity was accomplished by establishing the QT interval in the simultaneously recorded lead V_1 in which negative U waves were not commonly observed and then by using that QT interval to estimate the location of the TP segment in the remaining leads (3). The appearance of exercise-induced negative U waves in precordial leads including leads V_3 or V_4 was considered significant for anterior myocardial ischemia. The magnitude of positive U waves was also measured, with TP segment as the baseline. A prominent U wave was defined as >0.05 mV increase in the magnitude of a positive U wave along with decreased height of the T wave compared with U waves seen on electrocardiography before exercise (5). Typical cases with exercise-induced U wave alterations are shown in Figures 1 and 2.

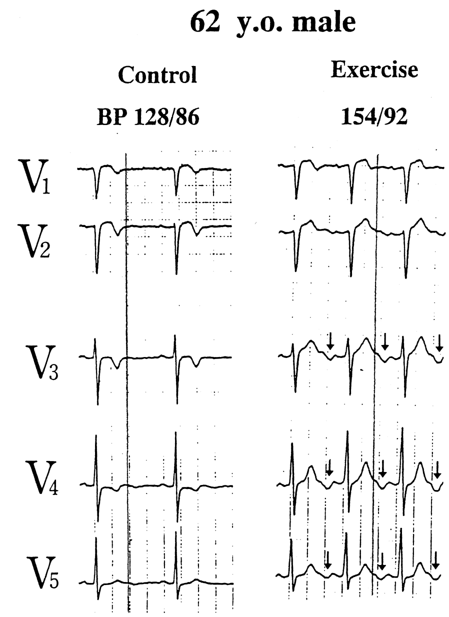

Figure 1. A typical ECG with exercise-induced negative U waves **(arrows)** during a chest pain attack in a 62-year-old male patient with exertional angina pectoris and previous anterior non-Q-wave myocardial infarction (group A). The **longitudinal line** shows the T-wave terminal determined by establishing a QT interval with simultaneously recorded lead V_1. Control: before treadmill exercise stress testing; Exercise: soon after exercise.

Catheterization procedures and angioplasty protocol. Before the catheterization procedures, written informed consent approved by the university ethics committee was obtained from each patient. Routine coronary arteriography after sublingual administration of nitroglycerin and left ventriculography were performed to determine the indica-

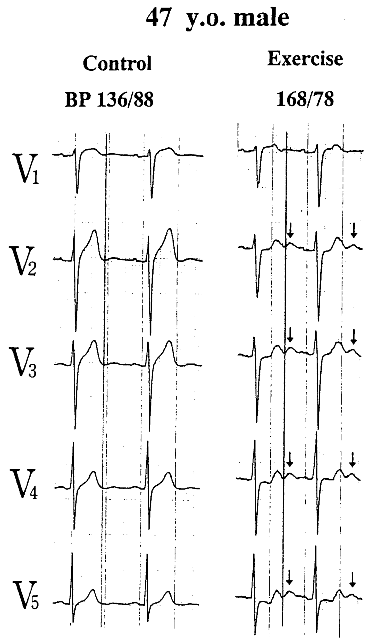

Figure 2. A typical ECG with exercise-induced prominent U waves **(arrows)** during a chest pain attack in a 47-year-old male patient with exertional angina pectoris (group A). The **longitudinal line** shows the T-wave terminal determined by establishing a QT interval with simultaneously recorded lead V_1. Control: before treadmill exercise stress testing; Exercise: immediately after exercise.

tion for coronary angioplasty, which was usually conducted one to three weeks later. Coronary stenosis was graded according to the criteria proposed by the American Heart Association (11). A significant stenosis of the coronary artery was defined as >75% diameter narrowing of a major artery branch. The degree of perfusion of the culprit coronary artery was graded on a scale of 0 to 3, as proposed by the TIMI (Thrombolysis in Myocardial Infarction trial) study group (12). The grade of collateral vessels was assessed according to the scale proposed by Rentrop et al. (13). Briefly, grade 0 = no observed collateral opacification; grade 1 = filling of the side branches to be perfused by collateral vessels without visualization of the main branch; 2 = partial filling of the main branch through collateral vessels; and grade 3 = complete filling of the main branch through collateral vessels. Three observers assessed the cineangiograms in a blinded fashion and reached a consensus. In the present study collateral vessels with grade 2 or 3 were classified as good collaterals.

In the case of coronary angioplasty, the coronary stenosis and presence of collateral vessels were evaluated by coronary arteriography immediately before the first balloon inflation. All patients were treated with 5000 U of heparin at the start of the procedure. Coronary angioplasty was performed with a standard right femoral approach. A 7F left or right Judkins femoral guiding catheter was advanced via the right femoral sheath into the ostium of the coronary artery. The deflated angioplasty balloon was then guided through the stenotic lesion. Following proper placement of the balloon catheter within the target area of stenosis, the balloon was inflated progressively until peripheral flow was interrupted. Each patient was asked whether anginal pain was present during balloon inflation. Standard 12-lead ECG was continuously recorded during balloon inflation using X-ray transparent carbon-fiber electrodes. The ST-segment shift was measured at 80 ms after the J point; ST-segment elevation or depression of ≥0.1 mV was considered significant for myocardial ischemia. All measurements were performed during 60 s of the first balloon inflation.

Statistical analysis. Data are expressed as mean ± standard deviation. Statistical analysis was done using the chi-square test with Yates' correction. Paired numerical data were compared by the Student paired *t* test. A p value $<$ 0.05 was considered statistically significant. Sensitivity was defined as the number of true positive tests × 100 divided by the sum of the true positive and false negative tests. Specificity was defined as the number of true negative tests × 100 divided by the sum of the true negative and false positive tests.

RESULTS

Exercise-induced U-wave changes and coronary arteriographic findings. During the treadmill exercise stress testing. U-wave changes in precordial leads appeared in 46 (37%) (group A) of the study patients, including 31 with negative U waves and 15 with prominent U waves. As shown in Table 1, there were no significant differences between the two groups in any of the following variables: gender, age and incidence of a prior MI. The incidence of severe angina of class III or IV was significantly ($p < 0.05$) higher in group A (52%) than in group B (32%) patients. The left ventricular ejection fraction was significantly ($p < 0.05$) higher in group B than in group A patients. In the coronary arteriographic findings, no significant differences were found in the incidence of multivessel disease or anterograde coronary flow across the lesion with TIMI grade 3 between the groups, although multivessel disease appeared to be rather more frequent in group A than in group B patients. However, good collateral vessels were significantly ($p < 0.05$) more frequently observed in patients in group A (70%) than in group B (43%).

In the diagnosis of well-developed collateral circulation by the finding of exercise-induced U-wave changes in precordial leads, the sensitivity was 48% (32/66) and the specificity was 76% (45/59) in the study patients with angina pectoris.

Exercise-induced U-wave changes and myocardial ischemia during coronary angioplasty. Twenty-three of group A patients and 40 of group B patients underwent coronary angioplasty for treatment of angina within three weeks of diagnostic coronary arteriography. These patients of group

JACC Vol. 35, No. 3, 2000
March 1, 2000:757–63

Table 1. Comparative Clinical and Coronary Arteriographic Findings in the Study Patients With (Group A) and Without (Group B) Exercise-Induced U-Wave Changes

	Group A		Group B
No. of patients	46		79
Women	11 (24%)		24 (30%)
Age (yrs)	62 ± 9		61 ± 11
Previous myocardial infarction	24 (52%)		28 (35%)
CCS class III or IV	24 (52%)	$p < 0.05$	25 (32%)
ST elevation during exercise test	9 (20%)		8 (10%)
Ejection fraction (%)	58 ± 11	$p < 0.05$	63 ± 10
Multivessel disease	29 (63%)		37 (47%)
Angina-related coronary artery			
LAD	29 (63%)		42 (53%)
RCA	10 (22%)		22 (28%)
LCX	8 (17%)		21 (27%)
Coronary arteriographic findings			
Anterograde flow: TIMI-3	19 (41%)		36 (46%)
Collateral vessels			
Good (grade 2 or 3)	32 (70%)	$p < 0.05$	34 (43%)

CCS = Canadian Cardiovascular Society (9), LAD = left anterior descending coronary artery; RCA = right coronary artery; LCX = left circumflex branch; TIMI = Thrombolysis in Myocardial Infarction trial (12).

A included 14 with negative U waves and 9 with prominent U waves observed during the exercise stress testing. Patient characteristics are shown in Table 2. During the first minute of coronary balloon occlusion, the incidence of observed significant ischemic ST-segment changes or deviation was 52% in group A, which was significantly ($p < 0.05$) lower

Table 2. Comparison of the Ischemic Status During Balloon Inflation in the Study Patients With (Group A) and Without (Group B) Exercise-Induced U-Wave Changes

	Group A		Group B
No. of patients	23		40
Women	5 (22%)		13 (33%)
Age (yrs)	59 ± 8		61 ± 10
Previous myocardial infarction	9 (39%)		11 (28%)
CCS class III or IV	10 (43%)		10 (25%)
Ejection fraction (%)	62 ± 9		61 ± 10
Multivessel disease	11 (48%)		14 (35%)
Coronary artery dilated			
LAD	14 (61%)		21 (53%)
RCA	3 (13%)		12 (33%)
LCX	6 (26%)		6 (15%)
Coronary arteriographic findings			
Anterograde flow: TIMI-3	12 (52%)		22 (55%)
Collateral vessels (Rentrop grade; see Ref. 13)			
good (grade 2 or 3)	15 (65%)	$p < 0.05$	14 (35%)
Ischemic findings during balloon inflation			
ST changes	12 (52%)	$p < 0.05$	34 (85%)
Elevation	6 (26%)		18 (45%)
Depression	6 (26%)		16 (41%)
Angina	13 (57%)	$p < 0.05$	32 (80%)
Both	11 (48%)	$p < 0.05$	30 (75%)
Neither	9 (39%)	$p < 0.05$	4 (10%)

CCS = Canadian Cardiovascular Society (9), LAD = left anterior descending coronary artery; RCA = right coronary artery; LCX = left circumflex branch; TIMI = Thrombolysis in Myocardial Infarction trial (12); Both: both ST changes and angina; Either: either ST changes or angina; Neither: neither ST changes nor angina.

than the 85% in group B. Also, the incidence of angina was significantly ($p < 0.05$) lower in group A (57%) than in group B (80%) patients during the procedure. Incidences of ST-segment elevation and depression were somewhat higher in group B than in group A, although differences between patient groups were not significant. The incidence of no myocardial ischemia of ECG ST deviation or angina during the first minute of coronary balloon occlusion was significantly ($p < 0.05$) higher in group A (39%) than in group B (10%) patients.

In predicting the absence of ECG myocardial ischemia of ST-segment deviation and angina during the first minute of coronary balloon occlusion, the sensitivity of the exercise-induced U-wave changes was 69% (9/13) and the specificity was 72% (36/50) in the study patients. The positive predictive value was 39% (9/23) and the negative predictive value was 90% (36/40).

DISCUSSION

The present study demonstrates that exercise-induced ECG U-wave alterations in the precordial leads are useful as a marker of a high-grade narrowing of any of the major coronary branches associated with good collateral vessels. Although these U-wave changes were not always observed, they had a relatively high specificity for the presence of well-developed collateral vessels. Of importance is that patients with these findings were frequently free from ischemic ECG ST deviation and angina during the first minute of coronary balloon occlusion, with four times higher incidence than those patients without the findings. Although the positive predictive value was not so high, exercise-induced U-wave changes appeared to be specifically predictive of well-functioning collateral vessels with flow reserve effective enough to protect completely against myocardial ischemia during the interruption of anterograde coronary blood flow. It should be emphasized that exercise-induced U-wave changes are obtained by standard exercise testing without any additional test, equipment, or cost, except for a detailed and careful analysis of the ECG (5).

Exercise-induced U-wave alterations as a marker for coronary narrowing and collateral development. Exercise-induced U-wave alterations have been shown to be a highly specific ECG marker localizing coronary artery narrowings (1,5,8). New negative U waves in precordial leads during exercise have been shown to be a useful marker for predicting proximal LAD lesions (1). Exercise-induced prominent U waves in the precordial leads are assumed as reciprocal changes for U-wave inversion in inferoposterior myocardial ischemia and are useful as a marker of narrowing of the left circumflex or right coronary artery (5). Chikamori et al. (5) reported that an increased magnitude of positive U waves during exercise alone showed a lower specificity for the left circumflex or right coronary artery lesion and, therefore, the height of T waves should be taken into account to improve the specificity of prominent U waves for inferoposterior ischemia. In the present study, exercise-induced prominent U waves in precordial leads were considered as positive only when they were accompanied by a decreased height in T waves, which can be regarded as reciprocal changes to ST-T changes in the inferoposterior wall.

Recently the significance of U-wave changes has been extended to patients with prior MI (4,8,14). Patients with anterior wall acute MI with negative U waves on the admission ECG were suggested to have a relatively smaller mass of necrotic myocardium (4). The relatively small amount of necrotic myocardium in patients with negative U waves is thought to be partly attributable to the presence of collateral circulation (4). Chikamori et al. (8) reported that a higher grade of LAD narrowing was angiographically documented in patients with anterior MI and exercise-induced U-wave inversion in whom myocardium in the territory of this artery was protected by well-developed collateral circulation. Exercise-induced negative U waves can also be regarded as an additional marker for the presence of ischemic but viable myocardium in patients with recent anterior MI.

Collateral function in patients with exercise-induced U-wave alterations. With the development of coronary angioplasty it became possible to evaluate the immediate consequences of abrupt coronary closure (13–15). In the present study, the exercise-induced U-wave changes were shown to be predictive of the absence of ischemic ECG ST deviation and angina during the first minute of coronary balloon occlusion. The clinical consequences of abrupt coronary closure are determined by an interaction between the location of the obstruction and the amount of recruitable collateral flow (14). The site of coronary obstruction determines the extent of myocardium at risk, whereas the amount of recruitable collateral flow determines the degree of protection of the risk area (14). The distal pressure in the occluded artery during balloon inflation was shown to be significantly higher in arteries with spontaneously visible and recruitable collaterals, which were frequently associated with the absence of ischemic ECG changes and chest pain during transient coronary occlusion (16). Patients with good collateral vessels can be specifically identified by the finding of exercise-induced U-wave changes.

Accordingly, patients with U-wave changes during exercise stress testing appear to be at low-risk for evolution of acute MI and hemodynamic instability upon acute coronary closure, although the impact of a permanent coronary occlusion resulting from an angioplasty complication remains to be determined in these patients, and assessment of collateral flow reserve or coronary wedge pressure is needed for the accurate prediction of the consequences of abrupt coronary closure (16–18). In the present study recruitable collateral circulation, which only develops during transient complete coronary occlusion, was not evaluated. Meier et al. (16) reported that the mean wedge pressure was rather higher and chest pain occurred during 30 s of balloon occlusion less frequently in patients with spontaneously visible collaterals than in those with recruitable collaterals, suggesting more effective protection against ischemia of the former.

Possible mechanisms or genesis of U-wave alterations. The mechanisms underlying the genesis of U waves are poorly understood (19,20). The mechanism of negative U waves is also unknown. In patients with variant angina and coronary spasm in the LAD, negative U waves without ST-segment elevation often appear in marginal ischemic zones or during the time of recovery from temporary ischemia (2,3). Fu et al. (21) reported that postischemic negative U waves appeared after the release of the ligation of the LAD in canine hearts. The appearance of negative U waves in the precordial leads, therefore, may indicate marginal ischemia or recovery from temporary ischemia and may be related to the regional heterogeneity of recovery from transient severe transmural ischemia or regional repolarization delay in ischemic but viable myocardium in the anteroseptal area. It is possible that the heterogeneity of repolarization is potentiated in the exercise-induced severely ischemic myocardium in the perfusion territory of a subtotally occluded coronary artery, partly protected by well-developed collateral vessels.

Recently Drouin et al. (22) provided evidence for the existence of subepicardial cells (M cells) in the human heart that contribute to heterogeneity of repolarization within the ventricular wall and consequently to the manifestation of the U wave on the ECG. These M cells are suggested to display a longer action potential duration than epicardial and endocardial cells and they exist in the deep subepicardial to midmyocardial layers of the ventricular free wall, representing approximately 30% of the ventricular mass (22). In the severely ischemic region, in terms of transmural changes in the action-potential duration, shortening of the action-potential duration in the inner layer of M cells would be prominent and prolonged owing to poor anterograde coronary perfusion. In contrast, it might be mild and of short duration in the outer subepicardial layer through well-developed collateral circulation in patients with exercise-induced U-wave alterations. The exercise-induced U-wave alterations we observed may reflect the potentiated heterogeneity of repolarization that would be greater in the presence of well-developed collaterals.

Conclusions. Exercise-induced ECG U-wave changes in the precordial leads including negative U waves and prominent U waves were seen in association with well-developed coronary collateral vessels in patients with exertional angina. In a considerable number of patients with exercise-induced U-wave changes, both ischemic ECG changes and angina were absent during coronary occlusion by an angioplasty balloon, suggesting that their angiographically well-developed collateral vessels were functioning in a sufficiently effective way to prevent resting myocardial ischemia completely. Low-risk patients for development of acute MI or hemodynamic instability upon abrupt closure of the stenotic coronary artery may be predicted by these exercise-induced U-wave alterations.

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